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(54) Title: PROSTHESES FOR THE ABDOMINAL WALL

(57) Abstract

To reduce the risk of infection in the reconstruction of the abdominal wall following hernia or other injury, a prosthesis comprises a porous material containing an antibacterial and/or other antimicrobial agent. The porous material preferably comprises a knitted polyester non-resorbable membrane, mesh or fabric substrate impregnated or enveloped with partially cross-linked (resorbable) gelatin and can be loaded with antimicrobial by soaking prior to suturing to the abdominal wall margin.

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PROSTHESES FOR THE ABDOMINAL WALL

This invention relates to prosthetic material for the repair of the abdominal wall in the case of injury or lesion caused, for example, by hernia, invasive infection or trauma. The invention also encompasses prostheses made from such material.

The invention addresses the general problem of providing prosthetic material for abdominal wall reconstruction. Contamination and infection are common problems encountered by surgeons in reconstructing the abdominal wall; these problems are exacerbated when foreign (usually synthetic) materials are present in a prosthesis, in that the risk of intraoperative contamination rises. Elek *et al.* (*Br. J. Exp. Pathol.* **38** 573-579 (1957)) showed that, when foreign materials are present, fewer microorganisms are required to produce a clinical infection: the foreign material acts as an adjuvant by decreasing the number of bacteria or other organisms necessary to produce an infection.

Both microporous polytetrafluoroethylene (PTFE), particularly as sold as the GORE-TEX® soft tissue patch and macroporous polypropylene mesh (particularly as sold as MARLEX®) have been used as prosthetic materials for abdominal wall reconstruction. Brown *et al.* (*Ann. Surgery* **201**(6) 705-711 (1985)) experimentally compared PTFE and polypropylene mesh abdominal wall prostheses and found a slight preference for the PTFE material. Antibiotics were administered systemically in these experiments.

In spite of the prior work that has been carried out in this area, there remains a low but significant rate of infection associated with synthetic tissue patches for abdominal wall reconstruction.

It has now been found that materials adapted to retain and deliver an antibiotic or other antimicrobial agent can also be used as abdominal wall prostheses.

According to a first aspect of the present invention, there is provided an abdominal wall prosthesis which is capable of retaining and delivering, an antimicrobial agent.

The prosthesis may comprise a composite structure of a resorbable porous material which absorbs and retains the microbiological agent. The composite may further comprise a non-resorbable mesh capable for use in abdominal wall reconstruction.

Goëau-Brissonnière *et al.* (*Ann. Vasc. Surgery* 5(5) 408-412 (1991)) used protein-impregnated porous materials containing rifampin as a vascular graft. In that case, the purpose of the protein-impregnation was to completely seal the graft, rather than specifically to provide a matrix for the rifampin. Graft sealing is not a requirement of abdominal wall prostheses, so the prior publication of Goëau-Brissonnière *et al.* does little to address the problem addressed by the present invention.

The porous material of this invention preferably comprises a substrate which is impregnated or otherwise associated with a suitable substance capable of retaining the antimicrobial agent. Preferably, the substance

capable of retaining an antimicrobial agent will not be a separate foil or film. Instead, the substance capable of retaining an antimicrobial agent impregnates the interstices of the substrate to form a composite prosthetic structure. Most preferably, the substance capable of retaining an antimicrobial agent will be completely resorbable in nature and the substrate will be either of synthetic or natural origin and will be non-resorbable once implanted into the patient. The substrate itself may be macroporous or microporous membrane, mesh or fabric. If a fabric, the fabric may be non-woven, woven, or preferably knitted. The fibre from which the fabric is prepared may be polymeric, for example PTFE, polypropylene or polyester, particularly polyethyleneterephthalate (PET).

The substance capable of retaining the antimicrobial agent may be a gel or have a gel-like or sponge-like open structure. In preferred embodiments of the invention, the substance is proteinaceous. The protein may be any suitable material having the desired properties for its intended use. In particularly preferred embodiments, the protein is gelatin (which is within the meaning of the term "protein" as it is used in this specification), ideally partially cross-linked as described in EP-A-0183365. The protein may also be a polyglycollic acid gel or other synthetic absorbable gel. A suitable and highly desirable protein-impregnated porous material is available from Vascutek Limited under the trade mark GELSEAL.

As stated above, it is also a preferred embodiment of the invention that the resorbable gelatin and the membrane mesh or fabric substrate be of a composite construction.

In Figures 1 and 2, the advantage of using a composite construction is clearly demonstrated. Specifically, in Figure 1, a non-composite, non-impregnated abdominal wall prothesis is shown. As demonstrated the antibiotic is forced to diffuse a great distance in order to surround and protect the mesh. During this diffusion process, antibiotic is lost and therefore lower concentrations of the antimicrobial agents is present at the site of prosthesis insertion. In the composite structure as shown in Figure 2, the antibiotic completely surrounds, the membrane, mesh or fabric due to the interlocking (impregnated) nature of the resorbable gelatin and the non-resorbable membrane, mesh or fabric. This allows the gelatin to completely envelope the substrate and dispense a high antimicrobial concentration around and into the mesh.

A significant advantage gained by utilising a composite of resorbable gelatin and a non-resorbable mesh as disclosed in this invention, is that the strength for the prosthesis will be provided by the non-resorbable membrane, mesh or fabric while the resorbable gelatin containing the antimicrobial agent will be resorbed by the patient, allowing for good tissue penetration into the mesh and hence a more secure prothesis.

There have been several prior attempts to construct a prosthesis or a net for implantation which includes treatment with some form of antibiotic. For instance, in US Patent No. 4,329,185 of Dimov *et al.* a biologically active polyamide net designed for implantation in the human body is prepared by a series of washing steps, one of which includes soaking the net in antibiotic and then rinsing and drying the net to a desired residual humidity

level. The net described, however, is not of a composite nature and hence the prolonged presence of antibiotic is not achieved. In Jenkins *et al.*, *Surgery* **94** 392-398 (1983), synthetic protheses were tested for their abilities to maintain strength, to be incorporated by surrounding tissues and to not stimulate adhesions. Whereas use of a variety of mesh was discussed, no mention of antimicrobial agents or a process by which the antimicrobials could be supplied to a prothesis prior to implant is mentioned. Additionally, an absorbable gelatin film in association with Marlex mesh was used as a separate film and not as an integral part of a composite Marlex/gelatin structure as seen in the present invention. The purpose of the separate gelatin film in the aforementioned publication was to prevent adhesions.

The antimicrobial agent of this invention may be an antiviral, an antibacterial, an antifungal or an antiprotozoal. Antibacterials include natural and semi-synthetic antibiotics as well as wholly synthetic antibacterials. Rifampin is an antibacterial which may be used to advantage in the present invention. Mixtures of different antimicrobial agents may be used. Sufficient antimicrobial agent will be present to provide an antimicrobial-effective dose of the agent in the conditions of use.

The porous material contains the antimicrobial agent. The antimicrobial agent may be absorbed in or adsorbed on the substrate, or even chemically bound to it in some convenient way, providing that its efficacy is not impaired.

Prostheses in accordance with the invention may be prepared by the following process, which itself forms part of the invention.

According to a second aspect of the invention, there is provided a process for the preparation of a prosthesis as described above, the process comprising loading the porous material with antimicrobial agent. The antimicrobial agent may be supplied in liquid form; if a solid at room temperature, it may be provided in the form of a solution, for example in water or normal saline. In such a case, loading will conveniently be achieved by contacting the porous material with the antimicrobial agent in liquid form, for example by spraying or, preferably, immersion.

By way of example, the gelatin-sealed knitted polyester graft available under the trade mark GELSOFT from Vascutek Limited may be soaked just before use in a 1mg/ml normal saline solution of rifampin at 37°C for 15 minutes. This is not to suggest that these conditions are limiting, but rather they are illustrative of the concentration and conditions that may be used to achieve a suitable loading.

The porous material itself may be prepared in any suitable way, for example as indicated in EP-A-0183365.

The principal intended use of prostheses in accordance with the invention is to reconstruct the abdominal wall of humans or, if required, other animals. The invention is therefore expected to be useful in a method of reconstructing the abdominal wall, the method comprising suturing or otherwise connecting a prostheses as described above to the abdominal wall margin.

According to a third aspect of the present invention, there is provided the use of an antimicrobial agent in the preparation of a prosthesis for the abdominal wall. Prosthesis material, which may be porous, will generally also be used in the preparation.

Preferred features of each aspect of the invention are for each other aspect, *mutatis mutandis*.

The invention will now be described by the following non-limiting example.

EXAMPLE

Gelatin-sealed knitted polyester graft patches were prepared in accordance with EP-A-0183365 and were soaked in a 1mg/ml normal saline solution of rifampin (RIFADINE®) at 37°C for 15 minutes.

Circular patches 2 cm in diameter containing Rifampicin are implanted subcutaneously in rabbits. The patches were either gelatin impregnated mesh (Gel+) or mesh only (Gel-) (i.e. composite resorbable/non-resorbable patches vs. non-composite non-resorbable patches). The patches were soaked in 20 mg/ml Rifampicin solution for 10 minutes. After the 10 minute soaking, the composite implants containing gelatin contained 740 µg/ml of rifampicin and the non-composite circular patches without gelatin (Gel-) contained only 490 µg/ml rifampicin. The patches were then surgically implanted into the rabbits and then explanted at varying time intervals and the remaining antibiotic then assayed. From Table I below, it can be seen that at 24 hours, 48 hours and 96 hours post-implantation, the mean loading of antibiotic was higher in the composite gelatin impregnated patches.

TABLE I

		Rabbit 01		Rabbit 02		Rabbit 03		Mean
	24H	Gel+	1,25	Gel+	1,54	Gel+	0,8	1,2 ± 0,37
		Gel-	0,32	Gel-	0,68	Gel-	0,23	0,41 ± 0,2
	48H	Gel+	0,14	Gel+	0,22	Gel+	0,25	0,2 ± 0,05
		Gel-	0,15	Gel-	0,15	Gel-	0,09	0,13 ± 0,0
	96H	Gel+	0,14	Gel+	0,21	Gel+	0,09	0,15 ± 0,0
		Gel-	0,07	Gel-	<0,07	Gel-	0,07	0,07

CLAIMS

1. An abdominal wall prosthesis capable of retaining and delivering an antimicrobial agent.

2. A prosthesis as claimed in claim 1, which comprises a porous material containing an antimicrobial agent.

3. A prosthesis as claimed in claim 2, in which the porous material comprises a substrate which is impregnated or otherwise associated with a suitable substance capable of retaining an antimicrobial agent.

4. A prosthesis as claimed in claim 3, wherein the substrate is a macroporous or microporous membrane, mesh or fabric.

5. A prosthesis as claimed in claim 4, wherein the fabric is non-woven, woven or preferably knitted.

6. A prosthesis as claimed in claim 3 or 4, wherein the fabric may be polymeric, polypropylene or polyester, most preferably polyethyleneterephthalate (PET).

7. A prosthesis as claimed in any one of claims 1 to 3, wherein the substance capable of retaining the antimicrobial agent is a gel or has a gel-like or sponge-like open structure.

8. A prosthesis as claimed in any one of claims 1 to 3 or 7 wherein the substance capable of retaining the antimicrobial agent is a synthetic absorbable gel, preferably a polyglycollic acid gel.

9. A prosthesis as claimed in any one of claims 1 to , 7 or 8, wherein the substance capable of retaining the antimicrobial agent is proteinaceous.

10. A prosthesis as claimed in claim 9, wherein the proteinaceous substance is gelatin, which preferably is partially cross-linked.

11. The prosthesis as claimed in any one of claims 1 to 10, wherein the substrate comprises a non-resorbable membrane, mesh or fabric and wherein the substance capable of retaining the antimicrobial agent is resorbable to allow good tissue penetration by impregnation of the substance capable of retaining the antimicrobial agent into the interstices of the substrate and wherein said substance capable of retaining the antimicrobial agent is not a separate foil.

12. The prosthesis as claimed in claim 11, wherein the non-resorbable substrate comprises a natural or biological material cross-linked to render it biostable and non-resorbable.

13. The prosthesis as claimed in claim 11, wherein the non-resorbable substrate comprises a synthetic membrane, mesh or fabric.

14. A prosthesis as claimed in any one of claims 1 to 11, wherein the antimicrobial agent comprises an antibacterial agent.

15. A process for the preparation of a prosthesis as claimed in any one of claims 1 to 14, the process comprising loading the porous material with antimicrobial agent.

16. The use of an antimicrobial agent in the preparation of a prosthesis for the abdominal wall.

FIG. 1.

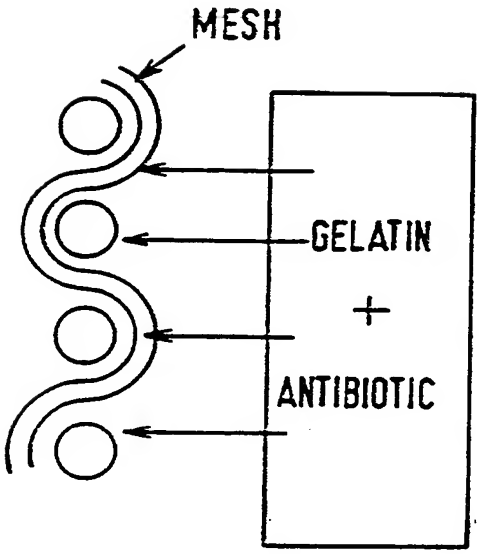
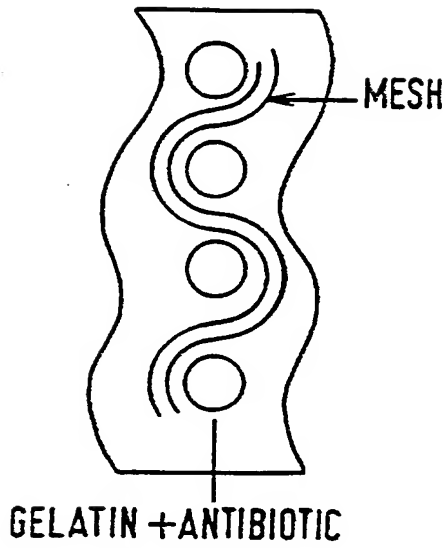


FIG. 2.



INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]B 95/01715

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L31/00 A61F2/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CARDIOVASCULAR SURGERY, vol. 2, no. 2, April 1994 pages 254-258, M. D'ADDATO ET AL. 'PREVENTION OF EARLY GRAFT INFECTION WITH RIFAMPICIN BONDED GELSEAL GRAFTS: A MULTICENTRE EXPERIMENTAL STUDY.' see the whole document ---	1-16
Y	SURGERY, vol. 94, no. 2, August 1983 pages 392-398, SCOTT D. JENKINS ET AL. 'A COMPARISON OF PROSTHETIC MATERIALS USED TO REPAIR ABDOMINAL WALL DEFECTS.' see abstract --- -/--	1-16

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer ESPINOSA, M

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	INTERNATIONAL ANGIOLOGY, vol. 11, no. 2, 1992 pages 113-116, A. FREYRIE ET AL. 'INTERACTION BETWEEN VASCULAR PROSTHESES AND RIFAMPICIN IN THE PREVENTION OF THE GRAFTS INFECTION. AN EXPERIMENTAL STUDY.' see abstract ---	1-16
A	EP,A,0 183 365 (J & P. COATS, LTD.) 4 June 1986 cited in the application see claims -----	1-16

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INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-183365	04-06-86	AU-B-	569645	11-02-88
		AU-B-	5059385	05-06-86
		CA-A-	1249490	31-01-89
		DE-A-	3586941	11-02-93
		IE-B-	59421	23-02-94
		JP-C-	1585374	31-10-90
		JP-B-	2011258	13-03-90
		JP-A-	61135651	23-06-86
		US-A-	4747848	31-05-88

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